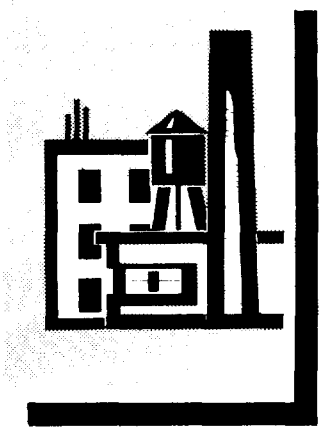
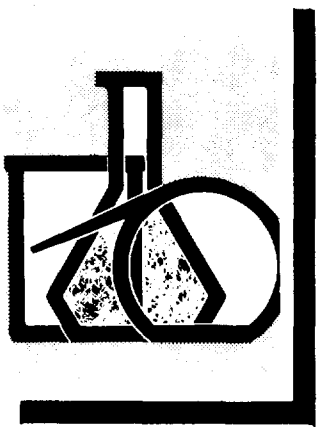
NIOSH

SPECIAL HAZARD REVIEW with CONTROL RECOMMENDATIONS





4,4'-METHYLENEBIS (2-CHLOROANILINE)

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

SPECIAL HAZARD REVIEW

WITH

CONTROL RECOMMENDATIONS

FOR

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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

PUBLIC HEALTH SERVICE

CENTER FOR DISEASE CONTROL

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH

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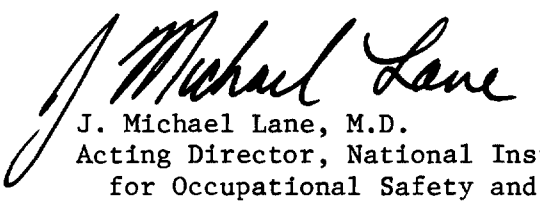
PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed to an ever-increasing number of potential hazards in their workplace. Pursuant to the fulfillment of this need, the National Institute for Occupational Safety and Health (NIOSH) has developed a reporting strategy intended to assist employers in providing personal protection for employees from exposure to carcinogenic, mutagenic, and teratogenic substances. This strategy involves the development of Special Occupational Hazard Reviews which serve to support and complement the other major criteria documentation activities of the Institute. It is the intent of a Special Occupational Hazard Review to document, from a health standpoint, the problems associated with a given industrial chemical or process. While Special Occupational Hazard Reviews are not intended to supplant the more comprehensive NIOSH Criteria Documents nor the less comprehensive NIOSH Current Intelligence Bulletins, they are nevertheless prepared in such a way as to be amenable to full regulatory usage if so desired. Dissemination of Special Occupational Hazard Reviews may be accomplished through appropriate trade associations, unions, industries, and members of the scientific community.



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I. INTRODUCTION

4,4'-Methylenebis(2-chloroaniline), more commonly referred to as MOCA, a registered trade name of the DuPont Company, has the formula C13H12C12N2. It has a molecular weight of 267.16. A yellow to light gray-tan, nearly odorless, crystalline solid, 4,4'-Methylenebis(2-chloroaniline) has a specific gravity of 1.44 at 24 C and a melting range of 100-110 C. Its vapor pressure is very low, i.e., less than 0.00001 mmHg at 25 C, and 0.000036 mmHg at 100 C. It is only slightly soluble in water, but is soluble in alcohol, ether, ketones, esters, organic solvents (e.g., trichloroethylene and toluene), and in lipids. 4,4'-Methylenebis(2-chloroaniline) is a weak base having the general chemical characteristics of primary aromatic amines. Synonyms for this compound include: 4,4'-methylene-bis(2-benzenamine); diamino-3-chlorophenylmethane; bisamine; di-(4-amino-3-chlorophenyl)methane; 4,4'-diamino-3,3'-dichlorodiphenylmethane; 3,3'-dichloro-4,4'-diaminodiphenylmethane; methylenebis(ortho-chloroaniline); and p,p'-methylenebis(ortho-chloroaniline). Common or trade names include: 4,4'-Methylenebis(2-chloroaniline); DACPM; MBOCA; MOCA; MCA; Curaline M; Curene 442; and Cyanaset (1,2).

It is commercially important as a curing agent for diisocyanate-based polymers (polyurethanes) and epoxy resin systems used in the manufacture of certain products, particularly integral-skin polyurethane semi-rigid foam as used for crash padding, and solid urethane rubber moldings such as gear blanks and industrial tires. 4,4'-Methylenebis(2-chloroaniline) is used to vary the hardness,

flexibility, and impact strength of these products. The first U.S. commercial production of 4,4'-Methylenebis(2-chloroaniline) is believed to have begun in 1956, using a process based on the reaction of formaldehyde and ortho-chloroaniline. Commercial-grade 4,4'-Methylenebis(2-chloroaniline) is available in the form of pellets or granules, and in a premixed compound with polyhydric alcohols (polyols). During the melting of solid 4,4'-Methylenebis(2-chloroaniline), when temperatures of about 200 C are used, the release of irritant and toxic vapors (primarily ortho-chloroaniline) may occur (1,2).

NIOSH estimated through a national survey that in the early 1970's approximately 55,000 U.S. workers were potentially exposed to 4,4'-Methylenebis(2-chloroaniline) (3). The majority of these workers were employed in small-to-medium sized establishments where occupational health services may not have been readily available.

Based on information presented by NIOSH (Appendix I), 4,4'-Methylenebis(2-chloroaniline) was one of 14 substances for which the Occupational Safety and Health Administration (OSHA) promulgated an emergency temporary standard on May 3, 1973. Final, individual standards for these substances were promulgated by OSHA on January 29, 1974. (4) On December 17, 1974, the standard for 4,4'-Methylenebis(2-chloroaniline) was remanded for procedural reasons by the 3rd Circuit Court of the U.S. Court of Appeals (Synthetic Organic Chemicals Manufacturer's Association vs. Brennen 506.F2d 385 1974). Subsequent to the court decision, the standard was deleted from the Code of Federal Regulations. Even though not enforceable as a Federal

standard, several states, including California, continued to enforce the standard under state law. The California Department of Health has recently held hearings to consider promulgation of environmental exposure limits for 4,4'-Methylenebis(2-chloroaniline).

In 1972, the American Conference of Governmental Industrial Hygienists (ACGIH) included 4,4'-Methylenebis(2-chloroanaline) as an experimental carcinogen in Appendix A of its Threshold Limit Values booklet (5) without a recommended environmental limit. The experimental carcinogen designation was applied by the ACGIH to industrial substances found to be of high potency for inducing tumors under experimental conditions in animals. In 1975, the ACGIH revised their designation for experimental carcinogens to be "Occupational Substances Suspected of Oncogenic Potential for Workers" and assigned 4,4'-Methylenebis(2-chloroaniline) a threshold limit value of 0.02 ppm with a skin notation. The documentation for this TLV was apparently not based on a consideration of the carcinogenic potential of this chemical but was established with the belief that this limit was "sufficiently low as to prevent systemic poisioning, provided skin contact is avoided." (6). The documentation included a warning that worker exposure by all routes should be reduced to a minimum in light of the warning of the potency for the chemical to induce tumors in animals (7). In 1974, the International Agency for Research on Cancer reviewed the information concerning 4,4'-Methylenebis(2-chloroaniline)'s potential carcinogenicity (1).

Additional information to that which appeared in the above sources is currently available. The following section provides a brief review

of the information available in 1973 (Appendix I), and a more detailed presentation of recent studies along with recommendations for control of workplace exposures to 4,4'-Methylenebis(2-chloroaniline).

II. HAZARD INFORMATION UPDATE

4,4'-Methylenebis(2-chloroaniline) was found to be "moderately toxic" when administered orally in single doses to male rats, with an Approximate Lethal Dose (ALD) of 1,000 mg/kg, (8). The report indicated that 4,4'-Methylenebis(2-chloroaniline) affected the kidneys of the experimental animals, and interfered with the hemopoietic system, as evidenced by the formation of methemoglobin and formation of red blood cells at sites other than the bone marrow. The clinical signs of toxicity at lethal doses included rapid and irregular respiration (eventually becoming labored), pallor, cyanosis, weakness, polyuria, and coma. Repeated sublethal oral doses (200 mg/kg) in the rat produced pallor, slight cyanosis, and a depressed rate of weight gain during treatment.

In a separate report (9) submitted from the same laboratory, the oral LD50 for 4,4'-Methylenebis(2-chloroaniline) (as a 10% solution in acetone (15)/peanut oil (85)) in male rats was reported as 750 mg/kg, with gross pathological changes including congested kidneys, an enlarged spleen, and hemorrhagic serosa of the stomach found in a few select animals.

Single 40 mg/kg doses of 4,4'-Methylenebis(2-chloroaniline) produced marked methemoglobinemia in dogs (10). The methemoglobin level returned nearly to normal 24 hours after the single dose. When administered daily in gradually increasing doses a slight methemoglobinemia and a macrocytic anemia developed, accompanied by fecal excretion of urobilinogen. The study also identified a major metabolite of 4,4'-Methylenebis(2-chloroaniline) in the dog urine,

5-hydroxy-3,3'-dichloro-4,4'-bis-aminodiphenylmethane. Clinical signs noted were weakness, vomiting, pallor and cyanosis.

Skin absorption studies on rabbits showed the ALD by this route to be greater than 5 g/kg, with pallor and weight loss observed (10). Repeated applications of 2.2 g/kg to the skin of rabbits resulted in pallor, cyanosis and hematuria during the 1st week of treatment only. No significant hematologic changes were found. Skin tests with guinea pigs indicated the compound to be mildly irritating, and not to produce allergic contact dermatitis (8).

An interim report of an 18-month feeding study conducted in NIOSH laboratories (11) confirmed the earlier reports reviewed in the 1973 NIOSH Hazard Review (Appendix I) that 4,4'-Methylenebis(2-chloroaniline) caused pulmonary and mammary gland adenocarcinomas, hepatocellular carcinomas, Zymbal gland tumors and hemangiosarcomas in male rats. 4,4'-Methylenebis(2-chloroaniline) was fed in graded doses in two different diets to male rats for 18 months; 250, 500, and 1,000 ppm in protein adequate (27% casein) and 125, 250, 500 ppm in protein deficient (8% casein). Groups of male rats which were fed the same two diets, but without 4,4'-Methylenebis(2-chloroaniline), served as controls. All surviving animals were killed 24 months after initiation of the chemical feeding. All animals that were started on the experiment were necropsied, including those that died during the experiment or were killed in a moribund state, as well as those killed at 24 months. A statistically increased incidence of the following types of tumors were observed in the 4,4'-Methylenebis(2-chloroaniline) treated animals regardless of the protein content of their diet:

adenocarcinoma of the lungs, hepatocellular carcinoma, mammary gland adenocarcinoma, and Zymbal gland tumors. There was a definite dose-response relationship, the larger the dose the greater the incidence of tumors. This interim report demonstrates that the effect of diet alone could not account for the carcinogenic activity of 4,4'-Methylenebis(2-chloroaniline).

The lowest concentration shown to produce all of the above tumor types in the protein adequate group was also the lowest concentration tested in that group, 250 ppm of 4,4'-Methylenebis(2-chloroaniline). The lowest concentration shown to produce pulmonary and mammary gland adenocarcinomas in the protein deficient group was 125 ppm of 4,4'-Methylenebis(2-chloroaniline) in the diet, again the lowest concentration tested in that group. The increased incidence of lung neoplasms in this group was statistically significant (6/100 vs. 0/100). The authors concluded that "In both diet groups the lungs were the most sensitive organs to the induction of neoplasms by 4,4'-Methylenebis(2-chloroaniline)."

In comparing the animals that received 500 ppm of 4,4'-Methylenebis(2-chloroaniline) in the protein deficient and protein adequate groups, the investigators concluded that protein deficiency caused an increased incidence of hepatocellular carcinomas. However, there was a lower incidence of mammary gland and lung adenocarcinomas in the protein deficient group as compared to the protein adequate group.

There was an increased incidence of hemangiosarcomas in the protein deficient group, 22% (4/18) in the 500 ppm group vs. 2% (1/49) in the

controls when comparisons were made between only those treated animals alive at the time the hemangiosarcomas were first diagnosed. The Fisher Exact Test yields a P value of 0.0164 (i.e., significant at the 0.05 level). The most current information, as yet unpublished, indicates the lifetime incidence rates to be 8% (4/50) in the treated, protein deficient group, and 1% (1/100) in the controls. The Fisher Exact Test yields a P value of 0.0425 (i.e., significant at the 0.05 level).

Another objective of the study was to determine whether or not the treated animals with tumors had more 4,4'-Methylenebis(2-chloroaniline) in their urine than the treated animals without tumors. The results were not consistent. There were significantly higher levels of 4,4'-Methylenebis(2-chloroaniline) (P less than 0.05) in the urine of animals with tumors in the 500-ppm dosage groups, regardless of diet, than in those animals in the same dosage groups without tumors. In the protein adequate, 500-ppm group, animals with tumors had a mean of 0.79 ppm in the urine after acid hydrolysis, while those without tumors had 0.50 ppm. In the protein deficient, 500-ppm group, the respective values were 2.19 ppm and 1.12 ppm. However, there were no statistically significant differences between similar groups at the other concentrations of 4,4'-Methylenebis(2-chloroaniline) tested. The urine was collected and analyzed 75-76 weeks after initiating the exposures and just before exposure was discontinued.

At the lowest concentration tested, 125 ppm, the mean concentration in the urine before acid hydrolysis was 0.09 ppm, and 0.63 ppm after acid hydrolysis. Although the significance of the observation is not known, it is interesting to note that equal or higher levels of

4,4'-Methylenebis(2-chloroaniline) have been reported in the urine of exposed workers (15, 16).

In work performed at Haskell Laboratory, urinary bladder tumors were produced in dogs given 4,4'-Methylenebis(2-chloroaniline) orally (12). Six female beagle dogs were given an oral dose of 100 mg by capsule, 3 days per week for the first 6 weeks, and then 5 days per week continuously for periods up to 9 years. The dose varied from 8 to 15 mg/kg body weight per day among the dogs. Six untreated female beagle dogs were used as controls. The test was terminated after 9 years of treatment, at which time all animals were killed and necropsied. The average plasma glutamic-pyruvic transaminase activity of the dogs fed 4,4'-Methylenebis(2-chloroaniline) was found to be higher than that of the controls during the 1st and last 2 years on test. During the 8th and 9th years, the urine sediment from the dogs given 4,4'-Methylenebis(2-chloroaniline) contained excessive numbers of erythrocytes, leukocytes, and epithelial cells. Some epithelial cells exhibited abnormalities that suggested neoplasia in the genitourinary tract. One treated animal died after 3.4 years from complications which were not considered by the investigators to be related to the test compound. One treated animal, killed after 8.3 years, had a papillary transitional cell carcinoma of the urinary bladder. The remaining four animals were killed after 9 years. Three of these had papillary transition cell carcinomas of the urinary bladder, and one had both a transitional cell carcinoman and an adenocarcinoma of the urethra. The urethral tumor had metastasized to the liver, but the papillary transitional cell carcinomas found in the other four dogs had

not invaded the muscle layers of the bladder wall, and had not metastasized. Since no urinary bladder tumors were found in the six control dogs, 4,4'-Methylenebis(2-chloroaniline) was judged to be carcinogenic for the urinary bladder of dogs under the conditions employed (P less than 0.025, Fisher's Exact Test, one tail). Three of five treated dogs contained hyperplastic nodules in the liver, with no such nodules in the six control dogs (P greater than 0.05, Fisher's Exact Test, one tail). This was considered by the investigators to be suggestive of an effect of 4,4'-Methylenebis(2-chloroaniline) treatment.

4,4'-Methylenebis(2-chloroaniline) has also been shown to be mutagenic in in vitro experiments. McCann et al, (13) reported 2.7 revertants per nmol (1050 revertants/plate) in the "Ames" test which utilizes Salmonella typhimurium as the test organism.

In approximately 22 years of industrial experience with the manufacture of 4,4'-Methylenebis(2-chloroaniline), DuPont has found no evidence of a carcinogenic effect in its workers (14). This is the only documentation of 4,4'-Methylenebis(2-chloroaniline)'s carcinogenic potential based on human experience which was found in the literature. It is noted in the report that the group studied was small, and that the length of time for which the workers were exposed to 4,4'-Methylenebis(2-chloroaniline) was too short to "permit statistically significant conclusions."

III. SUMMARY AND CONCLUSIONS

From the toxicologic information presented in APPENDIX I and the preceding information update, a profile of 4,4'-Methylenebis(2-chloroaniline)'s potentially hazardous properties can be developed. 4,4'-Methylenebis(2-chloroaniline) possesses the general toxicity characteristics of aromatic amines, and may, if introduced into the human body, produce cyanosis from methemoglobin formation (2). From an occupational health standpoint, there is greater concern for 4,4'-Methylenebis(2-chloroaniline)'s carcinogenic potential, evidence for which comes primarily from animal bioassays as well as in vitro mutagenicity studies. Results reported by five independent groups of investigators clearly demonstrate 4,4'-Methylenebis(2-chloroaniline) to be oncogenic in the rat, mouse, and dog. Ingestion of daily doses of 4,4'-Methylenebis(2-chloroaniline) by mice and rats has resulted in the appearance of cancers of the liver, kidneys, lungs, skin, and mammary glands (11, Appendix I). Subcutaneous injection of 4,4'-Methylenebis(2-chloroaniline) in rats produced liver and lung cancer in both sexes (Appendix I). Urinary bladder cancer was produced in female beagle dogs fed doses of 4,4'-Methylenebis(2-chloroaniline) which varied from 8 to 15 mg/kg body weight per day for up to 9 years (12). Further, 4,4'-Methylenebis(2-chloroaniline) is mutagenic in in vitro tests utilizing Salmonella bacteria (13).

Based on positive oncogenic results in three animal test species, NIOSH recommends that 4,4'-Methylenebis(2-chloroaniline) be treated as a potential occupational carcinogen. Because a significant route of

entry into the body is by skin absorption (1, 7, 15), efforts must be made to prevent skin contact with 4,4'-Methylenebis(2-chloroaniline), whenever possible. The use of protective clothing made of butyl rubber, neoprene, or spunbonded olefin has been shown to assist in the reduction of worker exposure through skin contact (14, 17).

Although research information is not yet available to demonstrate a quantitative relationship between skin absorption of 4,4'-Methylenebis(2-chloroaniline) and urinary levels in workers, industrial experience indicates that urinary monitoring is necessary as an adjunct to the monitoring of airborne 4,4'-Methylenebis(2-chloroaniline) in order to detect worker exposure as a result of absorption through the skin (15). The finding of 4,4'-Methylenebis(2-chloroaniline) in the urine demonstrates that exposure has occurred and can indicate work situations which need additional control efforts. Likewise, monitoring of workplace surfaces can identify where contamination problems exist and where the potential for workplace exposure is greatest. Details of one company's method of analysis for 4,4'-Methylenebis(2-chloroaniline) in urine are given in Appendix III. Detailed procedures for monitoring work surfaces for 4,4'-Methylenebis(2-chloroaniline) contamination are presented in reference 18 and in Appendix IV.

IV. CONTROL GUIDELINES

The National Institute for Occupational Safety and Health recommends that employee exposure to 4,4'-Methylenebis(2-chloroaniline) (MOCA) in the workplace, be controlled so that no worker will be exposed at concentrations in excess of 3 micrograms per cubic meter (μg/cu m) of air determined as a time-weighted average (TWA) concentration for up to a 10-hour workshift, 40 hour workweek, over a working lifetime. The recommended exposure level of 3 μg/cu m is the lowest level at which 4,4'-Methylenebis(2-chloroaniline) can be reliably measured at this time. The control guidelines contain recommendations for medical surveillance, informing employees of hazards, sanitation, work practices, labeling and posting, personal protective clothing and equipment, monitoring and recordkeeping.

While compliance with these recommendations should materially reduce the risk of developing cancer from 4,4'-Methylenebis(2-chloroaniline), no absolutely safe concentration can be established for a carcinogen at this time. The employer should regard the recommended permissible exposure level as the upper boundary of exposure, and make every effort to keep exposure by all routes as low as possible.

"Occupational exposure to 4,4'-Methylenebis(2-chloroaniline)" refers to any workplace situation in which it is manufactured, processed, used, or stored. Since 4,4'-Methylenebis(2-chloroaniline) is readily absorbed through the skin, all skin contact with it must be prevented.

Section 1 - Permissible Exposure Level

(a) Concentration

4,4' Methylenebis(2-chloroaniline) shall be controlled in the workplace so that the concentration of airborne 4,4'-Methylenebis(2-chloroaniline), does not exceed 3 μg/cu m in breathing zone air determined as a time-weighted average (TWA) concentration.

(b) Sampling and Analysis

The recommended environmental level represents the lowest concentration of 4,4'-Methylenebis(2-chloroaniline) reliably measurable by the recommended sampling and analytical methods selected. Procedures for the collection and analysis of air samples shall be as provided in Appendix II, or by any method at least equivalent in accuracy, precision, and sensitivity to the method specified.

Section 2 - Medical

Medical surveillance shall be made available to employees as outlined below:

(a) Preplacement

Preplacement examinations shall be made available to all workers occupationally exposed to 4,4'-Methylenebis(2-chloroaniline).

History and physical testing shall direct emphasis towards, but not be limited to, the pulmonary, renal, and hepatic systems, and shall include the personal and occupational history of the employee and family including genetic and environmental factors. Additionally, such factors as the current systems review, pregnancy, current treatment

with steroids or cytotoxic agents, and smoking habits should be considered.

(b) Laboratory and Other Special Tests

(1) 14" x 17" chest X-Ray

(2) Laboratory examinations to include:

Complete Blood Count;

Blood Chemistry tests to include serum glutamic oxalacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, total bilirubin, and gamma-glutamyl transpeptidase (GGTP);

Complete urinalysis to include microscopic examination and cytologic examination for neoplastic cells. Monitoring of urinary 4,4'-Methylenebis(2-chloroaniline) content is an important adjunct to the monitoring of airborne 4,4'-Methylenebis(2-chloroaniline) for the detection of worker exposure.

Additional tests such as sputum cytology may be considered by the examining physician.

Referral to appropriate medical specialists shall be considered if abnormalities are demonstrated by the above examinations or tests.

(c) Periodic examinations shall be made available on at least an annual basis and shall consist of those procedures listed in 2 (a) and (b) above.

(d) If the worker being examined has been employed directly in 4,4'Methylenebis(2-chloroaniline) production or handling for 10 years or longer, the laboratory portions of the above shall be repeated every 6 months. These examinations shall also be provided more frequently

if, in the opinion of the responsible physician, a worker shows abnormalities in the tests that warrant further evaluation.

(e) Pertinent medical records shall be maintained for all employees occupationally exposed to 4,4'-Methylenebis(2-chloroaniline) in the workplace. Such records shall be maintained for at least 30 years after termination of employment. These records shall be made available to the designated medical representatives of the Secretary of Health, Education, and Welfare, of the Secretary of Labor, of the employer, the employee, or former employee.

Section 3 - Labeling and Posting

A label shall be placed on each shipping and storage container of 4,4'-Methylenebis(2-chloroaniline), and all areas where there is occupational exposure to 4,4'-Methylenebis(2-chloroaniline) shall be posted.

All warning signs shall be printed both in English and in the predominant language of non-English-reading workers. Workers unable to read the labels and signs provided shall be informed verbally about hazardous areas and the instructions printed on labels and signs.

(a) Labeling

Each container of 4,4'-Methylenebis(2-chloroaniline) shall bear the following label:

4,4'-METHYLENEBIS(2-CHLOROANILINE)

(Trademark, Common Name, or Chemical Name)

WARNING!!

SUSPECT CANCER AGENT

DANGEROUS TO HEALTH IF INHALED OR SWALLOWED

Keep containers closed when not in use.

Wash thoroughly before eating, drinking, smoking, or using toilet.

AVOID SKIN CONTACT

(b) Posting

Entrances to areas where there is occupational exposure to 4,4'-Methylenebis(2-chloroaniline) shall be posted with signs bearing the legend:

CANCER SUSPECT AGENT

AUTHORIZED PERSONNEL ONLY

If respiratory protection is required in accordance with Section 4, the following statement in large letters shall be added to the required sign:

RESPIRATORY PROTECTION REQUIRED IN THIS AREA

Section 4 - Personal Protective Equipment and Clothing

(a) Respiratory Protection

(1) Engineering controls shall be used wherever needed to keep airborne 4,4'-Methylenebis(2-chloroaniline) concentrations below the recommended permissible exposure level. Compliance with this level may be achieved by the use of respirators under the following conditions only:

(A) During the time necessary to develop, install or test the required engineering controls or when such controls fail.

(B) For nonroutine operations, such as emergency maintenance or repair activities.

(C) During emergencies when air concentrations of 4,4'-Methylenebis(2-chloroaniline) may exceed the recommended permissible exposure level.

(2) When a respirator is permitted by paragraph (a)(1) of this section, it shall be selected and used pursuant to the following requirements:

(A) The employer shall ensure that no employee is exposed to 4,4'-Methylenebis(2-chloroaniline) because of improper respirator selection, fit, use, or maintenance.

(B) The employer shall establish and enforce a respirator program meeting the requirements of 29 CFR 1910.134 as amended.

(C) The employer shall provide respirators in accordance with Table I-1, and shall ensure that the employee uses the respirator provided when necessary.

(D) Respiratory protective devices described in Table I-1 shall be those approved under the provisions of 30 CFR 11.

(E) The employer shall ensure that respirators are adequately cleaned and maintained, and that employees are instructed and drilled, at least annually, in the proper use and testing for leakage of respirators assigned to them.

(F) Respirators shall be easily accessible and employees shall be informed of their location.

TABLE I-1

RESPIRATOR SELECTION GUIDE

Concentration of 4,4'-Methylenebis(2-chloroaniline)	Respirator Type Approved under Provisions of 30 CFR 11
Greater than 3 μg/cu m, or Emergency (entry into areas of unknown concentration for emergency purposes)	(1) Self-contained breathing apparatus with full facepiece operated in pressure-demand or other positive pressure mode.
	(2) Combination Type C supplied-air respirator with full facepiece operated in pressure-demand mode and auxiliary self-contained air supply.

(b) Eye protection

Eye protection shall be provided by the employer and used by the employees where eye contact with 4,4'-Methylenebis(2-chloroaniline) is likely. Selection, use, and maintenance of eye protective equipment shall be in accordance with the provisions of the American National Standard Practice for Occupational and Educational Eye and Face

Protection, ANSI Z87.1-1968. Unless eye protection is afforded by a respirator hood or facepiece, protective goggles (splash-proof safety goggles or cup-cover type dust and splash safety goggles) that comply with 29 CFR 1910.133(a)(2)-(a)(6)), or a face shield (8-inch minimum) shall be worn at operations where there is danger of eye contact with 4,4'-Methylenebis(2-chloroaniline) because of spills or splashes. If there is danger of 4,4'-Methylenebis(2-chloroaniline) striking the eyes from underneath or around the sides of the face shield, safety goggles shall be worn as added protection.

(c) Protective Clothing

Protective clothing shall be resistant to the penetration and to the chemical action of 4,4'-Methylenebis(2-chloroaniline). Clothing made of butyl rubber, neoprene, spunbonded olefin, or an equally effective material are suggested at this time. Protective clothing including gloves, bib-type aprons, boots, and overshoes, shall be provided for, and worn by, each employee during any operation that may cause direct contact with 4,4'-Methylenebis(2-chloroaniline). Supplied-air hoods or suits resistant to penetration by 4,4'-Methylenebis(2-chloroaniline) shall be worn when entering confined spaces, such as pits or storage tanks. In situations where heat stress is likely to occur, supplied-air suits, preferably cooled, are recommended. The employer shall ensure that all personal protective clothing is inspected regularly for defects, and is maintained in a clean and satisfactory condition.

Section 5 - Informing Employees of Hazards from 4,4' Methylenebis(2-chloroaniline)

(a) All new and present employees working where occupational exposure to 4,4'-Methylenebis(2-chloroaniline) may occur shall be informed orally and in writing of the hazards, appropriate emergency procedures, and proper conditions and precautions concerning its safe use and handling.

(b) Employers shall institute a continuing education program to ensure that all employees have current knowledge of job hazards, cleanup methods, maintenance, emergency and evacuation procedures. This program shall be held for all employees with occupational exposure to 4,4'-Methylenebis(2-chloroaniline) at intervals not greater than quarterly, or whenever there is a process change.

Section 6 - Work Practices

(a) Emergency Procedures

For all work areas where emergencies may occur, the employer shall ensure that employees are instructed in and follow the procedures specified below and any others appropriate to the specific operation or process.

(1) Procedures shall include at least prearranged plans for reentry into areas where 4,4'-Methylenebis(2-chloroaniline) leaks or spills have occurred for cleanup, decontamination, or maintenance purposes.

(2) Evacuation alarm systems shall be provided by the employer.

(3) Nonessential employees shall be evacuated from hazardous areas during emergencies. Perimeters of these areas shall be delineated, posted, and secured. Employees in adjacent areas shall be trained in evacuation procedures should these work areas become invloved.

(4) Only personnel trained in the emergency procedures and protected against the attendant hazards (by personal protective equipment and clothing as specified in Section 4) shall shut off sources of 4,4'-Methylenebis(2-chloroaniline), clean up spills, control and repair leaks, and fight fires in 4,4'-Methylenebis(2-chloroaniline) work areas. Proper protective respirators and clothing shall be worn by all personnel in the hazard area until concentrations of airborne 4,4'-Methylenebis(2-chloroaniline) have been demonstrated by monitoring to be below the recommended permissible exposure level.

(5) Firefighting procedures shall be established for areas where flammable materials are used with 4,4'-Methylenebis(2-chloroaniline). Chemical foam, carbon dioxide, or dry chemicals shall be used for firefighting in areas where 4,4'-Methylenebis(2-chloroaniline) is present.

(6) Showers, eyewash fountains, and washroom facilities shall be provided and so located as to be readily accessible to workers in all areas where skin or eye contact with 4,4'-Methylenebis(2-chloroaniline) is likely. If 4,4'-Methylenebis(2-chloroaniline) comes into contact with clothing or skin, contaminated clothing shall be

promptly removed and the skin washed thoroughly with soap and water. If 4,4'-Methylenebis(2-chloroaniline) gets into the eyes, the eyes shall be flushed immediately with copious quantities of water.

(7) Medical attention shall be provided for any workers involved in an emergency situation. Such exposures shall be reported to the immediate supervisor by the affected worker or a fellow employee.

(b) Control of Airborne 4,4'-Methylenebis(2-chloroaniline).

(1) Suitable engineering controls designed to limit exposure to 4,4'-Methylenebis(2-chloroaniline) to that prescribed in Section 1(a) shall be used.

The use of completely enclosed processes is the recommended method of control for 4,4'-Methylenebis(2-chloroaniline). Local exhaust ventilation may also be effective when used alone or in combination with process enclosure. When a local exhaust ventilation system is used, it shall be designed to prevent the accumulation or recirculation of ventilation control or process air in the workroom, to maintain 4,4'-Methylenebis(2-chloroaniline) concentrations below the permissible exposure level and to remove it from the breathing zone of employees. Exhaust systems discharging into outside air must conform with applicable local, state, and Federal air pollution regulations. Ventilation systems shall be subjected to regular preventive maintenance and cleaning to ensure effectiveness, which shall be verified by periodic airflow measurements at least quarterly. Measurements of system efficiency shall also be made immediately by personnel properly attired in specified protective equipment when any

change in production, process, or control might result in increased concentrations of airborne 4,4'-Methylenebis(2-chloroaniline). Tempered makeup air shall be provided to work areas in which exhaust ventilation is operating.

(2) In operations where premixed forms of 4,4'-Methylenebis(2-chloroaniline) can be substituted for other forms of this chemical or where these premixed forms would reduce the degree of worker exposure, such subsitution should be made.

(c) Handling of 4,4'-Methylenebis(2-chloroaniline), and Related Work Practices.

(1) Written operating procedures shall be developed and posted wherever 4,4'-Methylenebis(2-chloroaniline) is processed, handled, used, or stored.

(2) The employer shall ensure that safety showers, eyewash fountains, and other emergency equipment are in proper working order through regularly scheduled inspections performed by qualified maintenance personnel.

(3) Operating systems shall be inspected daily for signs of leaks by personnel attired in protective equipment (as specified in Section 4). All equipment, including valves, fittings, and connections, shall be checked for tightness and good working order. All newly made connections shall be checked for leaks by trained personnel attired in the prescribed personel protective equipment immediately after the system is placed in operation.

(4) If a leak occurs, it shall be corrected immediately. Work shall resume normally only after necessary repair or replacement has

been completed, the area has been ventilated, and the concentration of 4,4'-Methylenebis(2-chloroaniline) has been determined by monitoring to be below the permissible exposure level.

(5) Transportation and use of 4,4'-Methylenebis(2-chloroaniline) shall comply with all applicable local, state, and Federal regulations.

(6) When 4,4'-Methylenebis(2-chloroaniline) containers are being moved, or when they are not in use, appropriate covers shall be in place. Such containers shall be moved only with the proper equipment, and secured to prevent dropping or loss of control while moving.

(7) Process valves and fittings shall be readily accessible, and should not be located in pits and congested areas.

(8) Containers and systems shall be handled and opened with care. Approved protective equipment (as specified in Section 4) shall be worn while opening, connecting, and disconnecting 4,4'-Methylenebis(2-chloroaniline) containers and systems. Adequate ventilation shall be made available to prevent exposure of workers to 4,4'-Methylenebis(2-chloroaniline) when opening containers and systems.

(9) Personnel shall work in teams when 4,4'-Methylenebis(2-chloroaniline) in a quantity sufficient enough to create a hazard is first admitted to a system, while repairing leaks, or when entering a confined or enclosed space.

(d) Work Areas

(1) Regulated areas shall be established and access limited to authorized personnel where there is occupational exposure to 4,4'-Methylenebis(2-chloroaniline).

(e) Storage

(1) Storage facilities shall be designed to contain spills completely, and to prevent contamination of the workroom environment.

(2) Storage of 4,4'-Methylenebis(2-chloroaniline) in the same area with reactive metals, such as aluminum or magnesium, or other reactive chemicals, such as liquid ammonia, shall be prohibited.

(3) Storage containers shall be periodically inspected for leakage.

(4) Ventilation switches and emergency respiratory equipment shall be located outside storage areas in readily accessible locations that will be free of 4,4'-Methylenebis(2-chloroaniline) should an emergency occur.

(f) Spills, Leaks, and Waste Disposal

(1) If a leak or spill occurs, the following steps shall be taken:

(A) Evacuate all nonessential personnel from the area.

(B) Adequately ventilate the area where the spill or leak occurs.

(C) If in molten form, allow to crystallize; break up crystallized material and mechanically sweep up for disposal.

(D) If in solid form, collect spilled material (as above) for reclamation or disposal.

(2) Personnel entering the spill or leak area shall be furnished with appropriate personal protective equipment. All other personnel shall be excluded from the area.

(3) All wastes and residues containing 4,4'-Methylenebis(2-chloroaniline) shall be collected in 4,4'-Methylenebis(2-chloroaniline) resistant containers, and incinerated or buried in such a manner that no 4,4'-Methylenebis(2-chloroaniline) or toxic decomposition products are released into the environment.

(4) All workplace surfaces including process equipment shall be washed down with soap and water or an effective solvent on a periodic basis, the frequency of this periodic washdown shall be increased as indicated by the results of urinary monitoring and spot tests for work surface contamination. At no time shall the visible accumulation of 4,4'-Methylenebis(2-chloroaniline) be allowed.

Section 7 - Sanitation Practices

(a) Plant sanitation shall meet the requirements of 20 CFR 1910.141.

(b) Workers shall change into work clothing at the start of work and remove it at the end of each day. Appropriate locker rooms that provide separate storage facilities for street, work and protective clothing shall be provided.

(c) Clothing contaminated with 4,4'-Methylenebis(2-chloroaniline) shall be removed and placed in a closed container in a well-ventilated area for later disposal or decontamination. Employers shall require personnel who work with 4,4'-Methylenebis(2-chloroaniline) to shower before leaving the workplace at the end of each workday.

(d) Employers shall ensure that employees who handle 4,4'-Methylenebis(2-chloroaniline) wash their hands thoroughly with soap and water before eating, smoking, or using toilet facilities.

(e) The storage, dispensing, preparation, and consumption of food and beverages shall be prohibited in 4,4'-Methylenebis(2-chloroaniline) work areas. Also, smoking shall be prohibited in 4,4'-Methylenebis(2-chloroaniline) work areas, and smoking or related materials, i.e., snuff or chewing tobacco, shall not be carried into such areas.

(f) The employer shall ensure that personnel who launder and clean clothing or equipment contaminated with 4,4'-Methylenebis(2-chloroaniline) are aware of the potential hazards of exposure.

Section 8 - Monitoring and Recordkeeping Requirements

(a) Requirements set forth below apply to work areas where there is occupational exposure to 4,4'-Methylenebis(2-chloroaniline).

(1) An adequate number of personal air samples shall be collected monthly for the evaluation of the work environment with respect to the occupational exposure of employees.

(2) Environmental samples shall be taken when a new process is installed or changes made that may cause an increase in environmental conentrations. Significant increases in production, relocation of existing operations, interruption of normal maintenance schedules, or other functions that may increase airborne 4,4'-Methylenebis(2-chloroaniline) concentrations shall require resampling and analysis until two consecutive samples collected at least 1 week apart

demonstrate that the concentration is below the permissible exposure level.

(3) The minimum number of representative exposure determinations for an operation or process shall be based on variations in exposures and production schedules, and in accordance with the provisions prescribed in Section 1(b).

(4) If initial, periodic, or special evaluations indicate that the recommended permissible exposure level is exceeded, corrective engineering or other control measures shall be immediately instituted to ensure the safety of employees until a concentration below the recommended permissible exposure level is achieved. In such cases, sampling of each operation and work location shall be conducted until two consecutive employee exposure measurements, taken at least 1 week apart, reveal that the employee is not exposed to 4,4'-Methylenebis(2-chloroaniline) above the recommended permissible exposure level. Routine monitoring may then be resumed. Employers shall notify in writing, within 5 days, every employee who is found to be exposed to 4,4'-Methylenebis(2-chloroaniline) above the recommended permissible exposure level.

(b) Employers or their successors shall maintain records which shall include the sampling and analytical methods, and types of respiratory protection used, airborne concentrations found, and any additional information concerning exposure of employees to 4,4'-Methylenebis(2-chloroaniline). Each employee shall have access to data on his or her own environmental exposures. Pertinent records of occupational accidents and environmental exposures within the workplace

shall be kept for at least 30 years after termination of employment. Records of occupational exposures applicable to an employee should be included in the employee's medical records. These records shall be made available to the designated representatives of the Secretary of Health, Education, and Welfare, of the Secretary of Labor, of the employee or former employee, and of the employer.

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APPENDIX I

HAZARD REVIEW

OF

4,4'-METHYLENE-BIS(2-CHLOROANILINE)

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May 1973

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National Center for Disease Control
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4,4'-Methylene-bis(2-chloroaniline)

A preliminary report concerning the carcinogenicity of orally introduced 4,4'-methylene-bis(2-chloroaniline)* in rats was made by Steinhoff and Grundmann [1] in 1969. In 1970 these two investigators published a more extensive paper [2] of their completed findings. In the later paper the toxicity and carcinogenicity of 4,4'-methylene-bis(2-chloroaniline) was compared with that of 4,4'-diaminodiphenylmethane (DDM). Both of these compounds are used as hardeners or curing agents for epoxy resin systems and isocyanate-containing polymers. [2, 4, 7] Although commercial production of 4,4'-methylene-bis(2-chloroaniline) began in 1962, [3] DDM has been in production for over 25 years. [4] The investigators quote previous work to document the strong toxic effect of DDM on both rat and human liver as well as the carcinogenic effect on rat liver. Schoental [4] has also demonstrated the carcinogenicity of DDM on the rat liver. An accidental acute poisoning episode occured in 1965 in Great

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*4,4'-methylene-bis(2-chloroaniline) or 3,3'-dichloro-4,4'-diaminodiphenylmethane has been given the registered trademark, MOCA, by the E. I. du Pont de Nemours & Co., Inc.

Britain in which 84 persons became ill, some seriously, with jaundice following the consumption of bread accidentally contaminated with DDM. [5] In general, Steinhoff and Grundmann [1 and 2] considered 4,4'-methylene-bis(2-chloroaniline) to be less toxic but more carcinogenic than the non-chlorinated compound, DDM.

In their experiments Steinhoff and Grundmann [1 and 2] maintained fifty 100-day-old Wistar rats (25 male; 25 female) on a low protein diet containing 0.1 percent 4,4'-methylene-bis(2-chloroaniline) for 500 days. (Acute toxicity tests had earlier demonstrated the relative nontoxicity of the compound when all ten experimental animals in the study survived either an oral or a subcutaneous administration of a single dose of 5000 mg/Kg.) Control rats used in the chronic feeding experiment were maintained on an identical low protein diet excluding the test compound. At the termination of the 500-day experimental feeding period (total dose of 27 g/Kg body weight) the experimental animals were maintained on the control diet. The average life span for male rats was 565 test days, the average for females was 535 test days. The average life span for controls was 730 test days.

Of the 25 male animals, 23 died with tumors. Twenty-two animals had liver tumors and in 7 of these, primary lung tumors (not metastases) occured also. Two of the animals with liver tumors had lung metastases and one brain metastasy was observed. One animal without liver tumors exhibited "massive tumor permeation" of the lungs

and benign bladder papillomas were observed in one animal. The two tumor-free animals exhibited fatty livers with isolated necrosis and hemorrhages.

Of the 25 female animals, 20 died with tumors. Eighteen animals had liver tumors and in 4 of these animals, three also had primary lung tumors (not metastases) and one had mammary gland tumors. Two animals had lung tumors without liver tumors and 9 had benign mammary gland tumors. The investigators emphasized that lung tumors in rats are relatively rare. Of the 50 control animals only two mammary fibroadenomas were observed in female rats, although the average life span of the controls was longer than that of the experimentals.

In another set of experiments Steinhoff and Grundmann [6] injected a suspension of 94 percent pure, technical grade 4,4'-methylene-bis(2-chloroaniline) into 34 Wistar rats (17 males, 17 females). Subcutaneous injections of 500 or 1000 mg/Kg body weight were administered on the order of once a week, or at longer intervals, to a total dose of 25 g/Kg body weight. Twenty-two of the 34 animals died with a total of 29 malignant tumors. Nine animals had liver cell carcinomas which, in all but one such animal, were discovered in multiple locations. Primary lung carcinomas were formed in 7 animals with a multi-central distribution in 3 animals. In the 50 control animals (25 males, 25 females) a total of 13 malignant tumors at different sites were discovered, including one lung tumor. No liver tumors developed over an average life span of 1040 days compared to an

average life span of 778 days in experimentals. The investigators stated:

> "Thus, 3,3'-dichloro-4,4'-diaminodiphenylmethane exhibits a definite carcinogenic action in the rat, the liver and lungs being the main organs affected, even after subcutaneous administration and sufficient protein nutrition. However, a greater number of liver tumors appear in a shorter time after feeding the compound in a low-protein diet."

In 1972, Sherman and Zapp [7] presented investigations in which rats fed a normal diet, but containing 1000 ppm of 4,4'-methylene-bis(2-chloroaniline), for 18 months subsequently developed lung tumors with some spreading to the pleural cavity. The investigators also observed an increased incidence of liver tumors. When animals were maintained on a low protein diet containing the compound, the incidence and malignancy of both liver tumors (males) and mammary tumors (females) was found to increase.

A contemporary paper by the National Cancer Institute reports on the work of the Weisburgers [8] concerning the carcinogenicity of 4,4'-methylene-bis(2-chloroaniline) in mice and rats. Preliminary studies established the maximally tolerated dose of this compound in the diet was 1000 mg/Kg body weight in rats and 2000 mg/Kg body weight in mice. Control animals were maintained on Purina laboratory chow

during the chronic feeding investigations while equal numbers of experimental animals (25 male mice; 25 female mice; 25 male rats) were dosed at the above levels and other groups at half these levels. Tumors observed in experimental animals and absent in controls included: hepatomas in rats (4/19 effective rats at the high dose and 1/22 effective at the low dose); 1 glioma; 2 adenocarcinomas of the lung; 2 gastrointestinal adenocarcinomas; 1 ear duct tumor; 2 tumors of the urinary bladder; and 7 adenomata of the lung.

In female mice, hepatomas were observed in 50 percent of the animals at the high dose and 43 percent at the low dose. No hepatomas were observed in female control mice. In male mice there was no significant difference between experimentals and controls concerning the incidence of hepatomas. Although no vascular tumors (hemangiomas and hemangiosarcomas) were found in control mice, such tumors were observed in 40 percent of the males and 43 percent of the females receiving the high dose. At the low dose 23 percent of the males and none of the females were observed to develop vascular tumors. Malignant lymphomas which were common in control mice were not as common in the experimental animals.

It is interesting that three independent studies [6 through 8] have reported the development of lung tumors in rats exposed to 4,4'-methylene-bis(2-chloroaniline). As emphasized by the investigators of two of these studies, [6 and 8] the rat is not highly susceptible to lung tumor formation. The influence of diet is known to alter the

carcinogenic potential of various substances and diet apparently affects the carcinogenic potential of 4,4'-methylene-bis(2-chloroaniline), but the results of two studies [7 and 8] in which the experimental animals were maintained on a normal diet, to which the test substance was added, clearly demonstrate that the effect of diet, alone, is not sufficient to account for the oncogenic activity of 4-4'-methylene-bis(2-chloroaniline).

A single plant cohort study involving a group of 31 employees and an equal number of controls was published by Linch et al [3] in 1971. The length of exposure of the control group was not specified. When compared to the control group no significant findings were observed utilizing the Pap technique as a screening tool for the early identification of bladder cancer.

Medical records for 178 employees were reviewed for evidence of acute illnesses, specific systemic illnesses, chronic disease, and malignancy. With the exception of 4 individuals all individuals in this group had not been exposed to 4,4'-methylene-bis(2-chloroaniline) for the last 10 years. In this group the elapsed time since first exposure was:

a)	less than 10 years	-	no employees
b)	from 10 to 15 years	-	158 employees
c)	more than 15 years	-	20 employees

If the assumption is made that, of the group of 158 employees, 15 years had elapsed since the first exposure, and that no exposure had

occured for 10 years, then their total exposure was 5 years. Likewise, the total exposure of the group of 20 employees in which more than 15 years had elapsed since first exposure would be a maximum of approximately 2 years. Because of the short exposure durations of both groups, it should not be considered unusual that negative findings were reported since the known average latency period for development of occupational bladder cancer is approximately 20 years.

The fact that the rate of cancer deaths in the plant population was better than national cancer statistics is not surprising when consideration is given to the differences between the total U.S. population and the able working population of the plant.

These investigators considered the principal route of absorption to be other than respiratory and recommended biologic rather than air monitoring as the procedure of choice for exposure control.

Another industrial study involved the finding by Mastromatteo [9] in 1965 that two of six employees, both in their thirties, who had a mixed exposure to 4,4'-methylene-bis(2-chloroaniline), TDI and several isocyanate-containing resins developed urinary frequency with hematuria in addition to eye irritation, respiratory irritation with cough and tightness in the chest. The hematuria can best be related to the 4,4'-methylene-bis(2-chloroaniline) than to the other substances. The author considered the conditions to be mild but also

considered that exposure to this substance, primarily by dust inhalation, was the cause of the observed cystitis.

The results of the experimental animal studies involving rats and mice, as reported by three independent groups of investigators, [1,2,6,8] clearly demonstrate an active oncogenic role for 4,4'-methylene-bis(2-chloroaniline).

The absence of definitive industrial experience with only 2 reported studies, [3 and 9] and the positive findings in two animal studies by 3 independent investigators, preclude the elimination of 4,4'-methylene-bis(2-chloroaniline) as a human carcinogen.

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APPENDIX II

METHOD FOR SAMPLING AND ANALYSIS OF 4,4'-METHYLENEBIS (2-CHLOROANILINE) IN AIR

The NIOSH recommended methods for sampling and analysis of 4,4'-Methylenebis(2-chloroaniline) in air may be found in the NIOSH Manual of Analytical Methods (1), and the NIOSH Manual of Sampling Data Sheets (2).

The recommended methodology utilizes a two stage sampler consisting of a high efficiency glass-fiber filter, followed by a bed of silica gel sorbent to collect 4,4'-Methylenebis(2-chloroaniline) aerosol and vapor, and a high performance liquid chromatograph (HPLC) equipped with a UV detector for analysis. This method has been evaluated at levels as low as 0.15 μg per sample collected (50 l of air at 3.0 μg/m3) and found suitable (3).

While the recommended method is thought by NIOSH to be the best available at this time, it is still subject to further review and refinement. If research by NIOSH results in the development of improved methods for sampling and analysis of 4,4'-Methylenebis(2-chloroaniline) in air from the occupational environment, the information will be forwarded to the Department of Labor.

Monitoring for work surface contamination and for workers' urinary 4,4'-Methylenebis(2-chloroaniline) content should be routinely undertaken to supplement monitoring of workplace air. Industrial

experience has indicated that build-up of 4,4'-Methylenebis(2-chloroaniline) on workplace surfaces, even from low airborne levels may account for an increase of workers' urinary 4,4'-Methylenebis(2-chloroaniline) content above that which would normally be expected (15). Baseline data on individual workers' urinary 4,4'-Methylenebis(2-chloroaniline) content and for work surface contamination should be gathered under ideal working conditions, i.e., workers are provided with adequate protective clothing and equipment, work surfaces have been washed down (see Section 6 (f)), and airborne 4,4'-Methylenebis(2-chloroaniline) concentrations are at or below the recommended permissible exposure level. Assuming that the recommended airborne level for 4,4'-Methylenebis(2-chloroaniline) is being met, detection of the chemical at levels above the baseline in either urinary monitoring or spot tests would indicate a need for improving work practices and for washdown of work surfaces. Analysis for urinary 4,4'-Methylenebis(2-chloroaniline) content should be undertaken weekly at the end of the workshift. Spot tests should also be done on a frequent basis for the detection of work surface contamination and as confirmatory tests for unusual findings in urinary monitoring and following accidents, spills, leaks or any changes in the industrial process which might produce an increase in the accumulation of 4,4'-Methylenebis(2-chloroaniline) on workplace surfaces. Methodology for both spot tests and monitoring of urinary 4,4'-Methylenebis(2-chloroaniline) content have been developed and used successfully by LASL (17) and the DuPont Company (Appendix III and IV).

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APPENDIX III

METHOD FOR DETERMINATION OF MOCA (TM) IN URINE BY GAS CHROMATOGRAPHY*

I. Scope and Application

This is a method for the determination of low levels of methylenebis-(ortho-chloroaniline) (MOCA) in ethyl ether extracts of urine samples.

The method can also be used to measure the approximate concentration of LD-813 present in urine. The LD-813 level can be estimated by measuring the MOCA content and dividing the result by 0.4.

The method was developed using a Hewlett-Packard 5750 gas chromatograph equipped with a dual flame ionization detector and a 1-mv recorder.

Component	Formula	Range of Method, μg	Expected composition, μg
Chloroform	CHCl3	-	Solvent
Triphenylamine	(C6H5)3N	-	Internal Standard
MOCA Derivative	C17H10O2N2Cl2F6	2-28	5

II. Sensitivity, Precision, and Accuracy

The precision of this method at the 95% confidence limits, for ten degrees of freedom, is ± 0.02 mg/liter at the 0.1 mg MOCA/liter urine level and ± 0.14 mg/liter at the 0.5 mg MOCA/liter urine level. This precision was determined by two technicians on two separate days.

The lower limit of detection is 0.04 mg MOCA/liter of urine. This sensitivity was determined by adding decreasing amounts of MOCA to urine, extracting with ether, and analyzing.

Samples were prepared at 0.1 and 0.5 mg/liter levels on five separate days and analyzed. Accuracy was within the limits of the precision.

III. Safety Precautions

1. Ethyl ether is extremely flammable. Handle with care in a well-ventilated hood away from sparks and flames. The TLV is 400 ppm.

*This method is one employed by E.I. duPont de Nemours and Company, Inc., Elastomer Chemical Department, Wilmington, Delaware 19898, and is identified by their Code No. U860.5200S, 30 July 1975.

2. Trifluoroacetic anhydride is a poisonous lachrymator. Avoid inhalation of vapors and skin contact. If spilled on the skin, flush immediately with copious quantities of cold water.

3. Chloroform is poisonous. It should be handled with adequate ventilation. Avoid repeated or prolonged contact with the skin. The TLV is 25 ppm.

4. Ethyl alcohol is a flammable material. Handle in a well-ventilated hood away from sparks and flames. The TLV is 100 ppm.

5. Handle triphenylamine with care as it is an aromatic amine. Keep off skin; handle in well-ventilated area.

6. MOCA is a "cancer-suspect agent" and is regulated by the Department of Labor, Occupational Safety and Health Administration's "Carcinogens - Occupational Health and Safety Standards." As required by this Standard, the following are posted at the regulated area: definition of the regulated area, handling procedures, decontamination procedures, waste disposal, emergency procedures, regulated area entry log sheets, and inventory log sheets. Only those persons specifically designated to work with MOCA are allowed to enter the regulated area.

7. The volumetric flask used in the preparation of MOCA standard solution must be charged with MOCA inside the designated hood area. For weighing purposes the flask must be decontaminated with acetone prior to removal from the hood. Dispose of decontamination rinsings into containers approved for this purpose.

IV. Reagents

1. Chloroform, reagent grade

2. Ethyl ether, anhydrous ACS grade

3. Trifluoroacetic anhydride, Eastman white label No. 7386**

4. Triphenylamine, Eastman white label No. 1907

5. Trisodium phosphate, 1% aqueous solution

6. Nitric acid, 1 + 1.

7. Citric acid, 30% aqueous solution

8. Ethyl alcohol, absolute, U.S.P.

9. Triphenylamine Internal Standard Solutions

**The mentioning of product names does not constitute endorcement by the Department of Health, Education, and Welfare.

a. Internal Solution A

1) Weigh (to the nearest 0.0001 g) 0.045 - 0.055 g triphenylamine (TPA) into a 100-ml volumetric flask.

2) Dilute to volume with chloroform and mix.

3) Calculate TPA concentration as follows:

Conc TPA Solution A, μg/ml - wt TPA, g x 10,000

b. Internal Solution B

1) Add (pipet) 4.0 ml of TPA Standard Solution A to a 100-ml volumetric flask.

2) Dilute to volume with chloroform and mix.

3) Calculate TPA concentration as follows:

Conc TPA Solution B, μg/ml = Conc TPA Solution A x 0.04

10. MOCA Standard Solutions (See Safety Precautions, Section III)

a. MOCA Standard Solution A

1) Weigh (to the nearest 0.0001 g) 0.0045 - 0.0055 g of MOCA into a 100-ml volumetric flask.

2) Dilute to volume with ethyl alcohol and mix.

3) Calculate MOCA concentration as follows:

Conc MOCA Solution A, μg/ml = wt MOCA, g x 10,000

b. MOCA Standard Solution B

1) Add (pipet) 10 ml of MOCA Standard Solution A to a 100-ml volumetric flask.

2) Dilute to volume with ethyl alcohol and mix.

3) Calculate MOCA concentration as follows:

Conc MOCA Solution B, μg/ml = Conc MOCA Solution A x 0.1

Note: MOCA Solution B contains approximately 5 μg/ml

c. MOCA Standard Solution C

1) Add (pipet) 50 ml of MOCA Standard Solution A to a 100-ml volumetric flask.

2) Dilute to volume with ethyl alcohol and mix.

3) Calculate MOCA concentration as follows:

Conc MOCA Solution C, μg/ml = Conc MOCA Solution A x 0.5

11. Sodium bicarbonate, 10% aqueous

12. Brilliant Yellow indicator strips

13. MOCA recrystallized to a 109 C minimum melting point

V. Apparatus

1. Bottles, specimen, milk dilution plain, Corning No. 1365

2. Caps, gum rubber, Davol "Sani-Tab" No. 268, 1-1/2 in. od

3. Separatory funnel, Squibb, 125-ml with TEFLON(TM) stopcock

Clean all glass apparatus by soaking for a minimum of one hour, preferably 16 hours, in 1% aqueous trisodium phosphate. Rinse with distilled water, 1 + 1 nitric acid, and distilled water.

VI. Column Packing

Partitioning liquid	OV-1
Source	Supelco, Inc., Bellefonte, Pa.
Parts by weight liquid per 100 parts support	11.1%
Support	Supelcoport
Source	Supelco, Inc., Bellefonte, Pa.
Mesh size	80 - 100

This column packing is sold commercially by Supelco, Inc., Supelco Park, Bellefonte, Pa. 16823

VII. Operating Conditions (See Note 1)

Column size	5 ft x 0.085 in. (id)
Column packing	10% OV-1 on Supelcoport, 80 - 100 mesh
Column material	Stainless steel
Column temperature	280 C isothermal
Carrier gas	Argon
Flow rate	7 ml/min
Detector temperature	290 C
Injection port temperature	290 C
Sample size	3 μl

Component	Actual Retention Time Min	Sec	Relative Retention Time*	Sensitivity
Chloroform		40	0.2	128 x 10(4)
Triphenylamine	3	30	1.0	128 x 1
MOCA derivative	8	25	2.4	16 x 1

*Relative to TPA

VIII. Interferences

Any material having a chromatographic elution time identical to the MOCA derivative will yield high results. High MOCA analyses have been reported by individuals under medication at the time of sampling. Some medications interfere grossly with the determination. Each medication should be studied individually for its possible interference with this determination. The following medications have been evaluated.

Gross Interference	Slight Interference	No Interferences
Darvon (TM)	Talwin (TM)	Ananase (TM)
Aldoril (TM)	Norgesic (TM)	Tylenol (TM)
		Citrated Caffeine
		Nyquil (TM)
		Contac (TM)
		Anacin (TM)
		Anahist (TM)
		Aspirin
		APC

Effects of inhalation or ingestion of industrial chemicals upon this determination are not known. Some indication of possible interference can be obtained by adding the known chemical to human urine and analyzing the sample according to the method. This procedure, however, does not take into account any possible metabolite of the chemical under study. Materials tested under these conditions and found to produce chromatographic peaks in the MOCA derivative region and possibly interfere include HVA-2, POLYAC, and ZENITE. The following do not interfere: ADIPRENE, A-101 oil, Diak 3, Glycol E, HYLENE MP, HYLENE W, Micro-cel E, NA-22, PACM, VITON, HYLENE TRF, IML-1, CAYTUR 4, hexamethylenediamine, dimethylethanolamine, dimethoxyethyl phthalate and dimethylformamide.

IX. Procedure

A. Sample Preparation

1. Clean all glassware as directed in Section V, Apparatus.

2. To the clean specimen bottle, add (grad cyl) 2 ml of 30% citric acid stabilizer solution. Seal the bottle with the "snap-on" rubber cap.

3. After the urine specimen has been placed in the bottle, seal the bottle with the cap as quickly as possible. Mix the solutions by swirling.

   The urine solution can be stored for several hours in its stabilized form; however, the time should be kept as short as possible to prevent degradation of the MOCA. See Section XII, Calibration for degradation rate of MOCA in stabilized urine.

4. Add (grad cyl) 50 ml stabilized urine sample to the 125-ml separatory funnel.

   Start standard by adding 1 ml of MOCA Standard Solution B to 50 ml of uncontaminated urine; swirl to mix and let stand 5 min.

5. Add (pipet) 10 ml of ethyl alcohol and shake to mix. Let solution stand 5 min.

6. Add (grad cyl) 5 ml of 10% sodium bicarbonate solution and shake to mix, venting the CO2 through the stopcock.

7. Test the urine with Brilliant Yellow indicator paper. If the solution is not definitely alkaline, add additional 1-ml

increments of bicarbonate until a positive test is obtained.

Brilliant Yellow paper changes to a bright red color in an alkaline medium.

8. Add 50 ml ethyl ether and shake steadily for 2 min.

Do not use intermittent shaking as an emulsion will result.

9. Let the solutions stand for 5 min to permit complete phase separation. Drain off the lower urine layer and discard.

10. Swirl the funnel to clear the interface and remove the last few ml of urine

11. Add (grad cyl) 5 ml of 10% sodium bicarbonate solution; shake for 10 sec (venting through the stopcock).

12. Let the solutions settle for 5 min and drain off the bottom layer.

B. Analysis for MOCA

1. Drain ether layer into a 30- x 80-mm vial. Evaporate the ether to dryness by blowing a stream of dry nitrogen into the vial.

Do not use air to evaporate the ether. A hot water bath may be used to hasten evaporation.

2. Add (medicine dropper) 1 ml trifluoroacetic anhydride. Allow the materials to react for a minimum of 10 min at room temperature.

3. Evaporate the contents of the vial to dryness using dry nitrogen.

4. Add (pipet) 1.0 ml TPA internal Standard Solution B and mix thoroughly.

5. Inject 3-μl samples into the chromatograph. (See Figure I)

Before analyzing any urine samples, condition the column by injecting several 6-μl samples of MOCA standard sample F. Preconditioning of the column is necessary to minimize adsorption and loss of MOCA.

X. Calculations

1. Determine the areas for MOCA and TPA using the formula:

Peak area, mm2 = peak height x width at 1/2 height x attenuation

2. Calculate the area ratio for MOCA

$$\text{Area ratio MOCA} = \frac{\text{area MOCA mm2}}{\text{area TPA mm2}}$$

3. Determine the weight ratio for MOCA from the calibration curve, Figure II. (See Section XII, A.)

4. Calculate μg MOCA as follows:

$$\text{MOCA, } \mu\text{g} = \text{wt ratio MOCA x conc TPA Soln, } \mu\text{g/ml}$$

$$\text{MOCA extracted, mg/liter} = \frac{\mu\text{g MOCA}}{\text{ml sample}}$$

5. Correct MOCA concentration for extraction efficiency as follows:

MOCA, mg/liter = MOCA extracted, mg/liter x Reciprocal Extraction Factor, see Figure III.

Report results to nearest 0.01 mg/liter.

XI. Column Standardization

Inject a sample which has been prepared according to the procedure (Section IX). Each peak must have the approximate retention time (± 5%), shape, and degree of resolution as those in a standard chromatogram. If these requirements are not met, check the operating conditions and/or replace the column.

XII. Calibration

A. Calibration Curve

1. Preparation of MOCA Stock Solution 1 (See Safety Precautions, Section III)

   a. Weigh (to the nearest 0.0001 g) 0.045 - 0.055 g MOCA into a 100-ml volumetric flask.

   b. Dilute to volume with ethyl ether.

   c. Calculate MOCA concentration as follows:

   Conc MOCA Soln 1, μg/ml = wt MOCA, g x 10,000

2. Preparation of MOCA Stock Solution 2

a. Pipet 10 ml MOCA Stock Solution 1 into a 1-liter volumetric flask.

b. Dilute to volume with ethyl ether.

c. Calculate MOCA concentration as follows:

Conc MOCA Soln 2, μg/ml = conc Soln 1, μg/ml x 0.01

3. Preparation of Standard Samples

a. Into five 30- x 80-mm vials, add (pipet) MOCA Stock Solution 2 as shown below:

Standard Sample	MOCA Stock Solution 2
A	0.4 ml (approximately 2 μg)
B	1.0 (approximately 5 μg)
C	2.0 (approximately 10 μg)
D	3.0 (approximately 15 μg)
E	4.0 (approximately 20 μg)
F	5.0 (approximately 25 μg)

b. Evaporate the standard samples to dryness under a nitrogen blanket. A water bath at 40 C may be used to aid evaporation.

c. Add (pipet) 1 ml trifluoroacetic anhydride and allow to react for 10 min.

d. Evaporate to dryness under a nitrogen blanket.

e. Add (pipet) 2 ml of triphenylamine Stock Solution B to each of the five standard samples.

f. Calculate weight ratio of MOCA/TPA in each standard sample, using the formula:

$$\text{Wt ratio MOCA/TPA} = \frac{\text{Conc MOCA Soln 2 x vol Soln 2 added, ml}}{\text{Conc TPA Soln x 1 ml}}$$

4. Preparation of Calibration Curve

a. Inject 3-μl sample of each standard sample into the chromatograph. Condition the column before injecting any samples (see Note 1).

b. Measure peak areas of MOCA derivative and TPA using formula:

Peak area mm2 = peak height x width at 1/2 height x attenuation.

c. Calculate area ratio of MOCA derivative and TPA as shown:

$$\text{Area ratio MOCA} = \frac{\text{area MOCA mm2}}{\text{area TPA mm2}}$$

d. Plot area ratio versus weight ratio for MOCA and draw a curve through the points. (See Figure II.)

B. Extraction Factor

1. Preparation of MOCA/Urine Solutions

a. Add (grad cyl) 50 ml of stabilized, uncontaminated urine to 20 separatory funnels.

b. Add (pipet) 1 ml of MOCA Standard Solution B to each of 10 funnels and 1 ml (pipet) of MOCA Standard Solution C to the other 10.

c. Swirl to mix and let stand 5 min.

2. Preparation of Extraction Curve

a. Proceed starting from Section IX, A, step 5.

b. Determine mg/liter MOCA extracted from Section X, Calculation.

c. Calculate Reciprocal Extraction Factor as follows:

$$\text{Reciprocal Extraction Factor} = \frac{\mu\text{g/ml MOCA Standard Soln x 1 ml}}{\text{mg MOCA Extracted}}$$

d. Average Extraction Factors for each solution.

e. Plot mg/liter MOCA Extracted versus Extraction factors and draw a curve through the points. (See Figure III.)

C. Degradation Rate

1. Preparation of MOCA/Urine Solutions

a. Add (grad cyl) 50 ml of stabilized, uncontaminated urine to 14 specimen bottles.

b. Into seven bottles, add 1 ml of MOCA Standard Solution B and into the other seven add 1 ml of MOCA Standard Solution C.

c. Swirl to mix and store at room temperature

d. Analyze for MOCA, mg/liter on 1,2,3,4,5,9, and 13 days, starting with Section IX, A, step 5.

2. Preparation of Degradation Curve

a. Plot MOCA, mg/liter versus time and draw a curve through the points. (See Figures IV and V.)

XIII. Notes

1. Condition the column daily by injecting several 6-μl samples of MOCA derivative from standard sample F. The column must be conditioned before any urine samples are run for MOCA content.

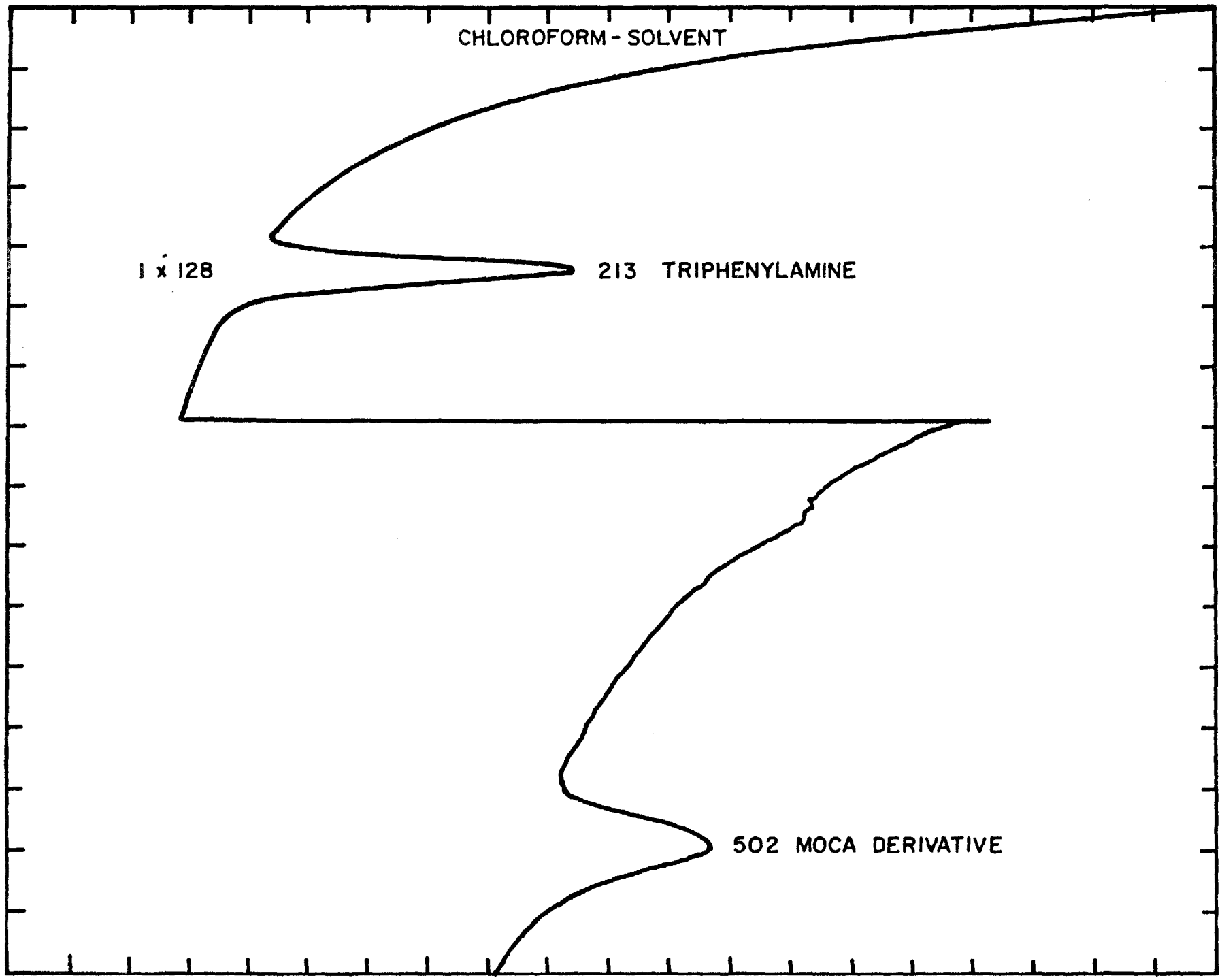

Figure 1 MOCA elution curve

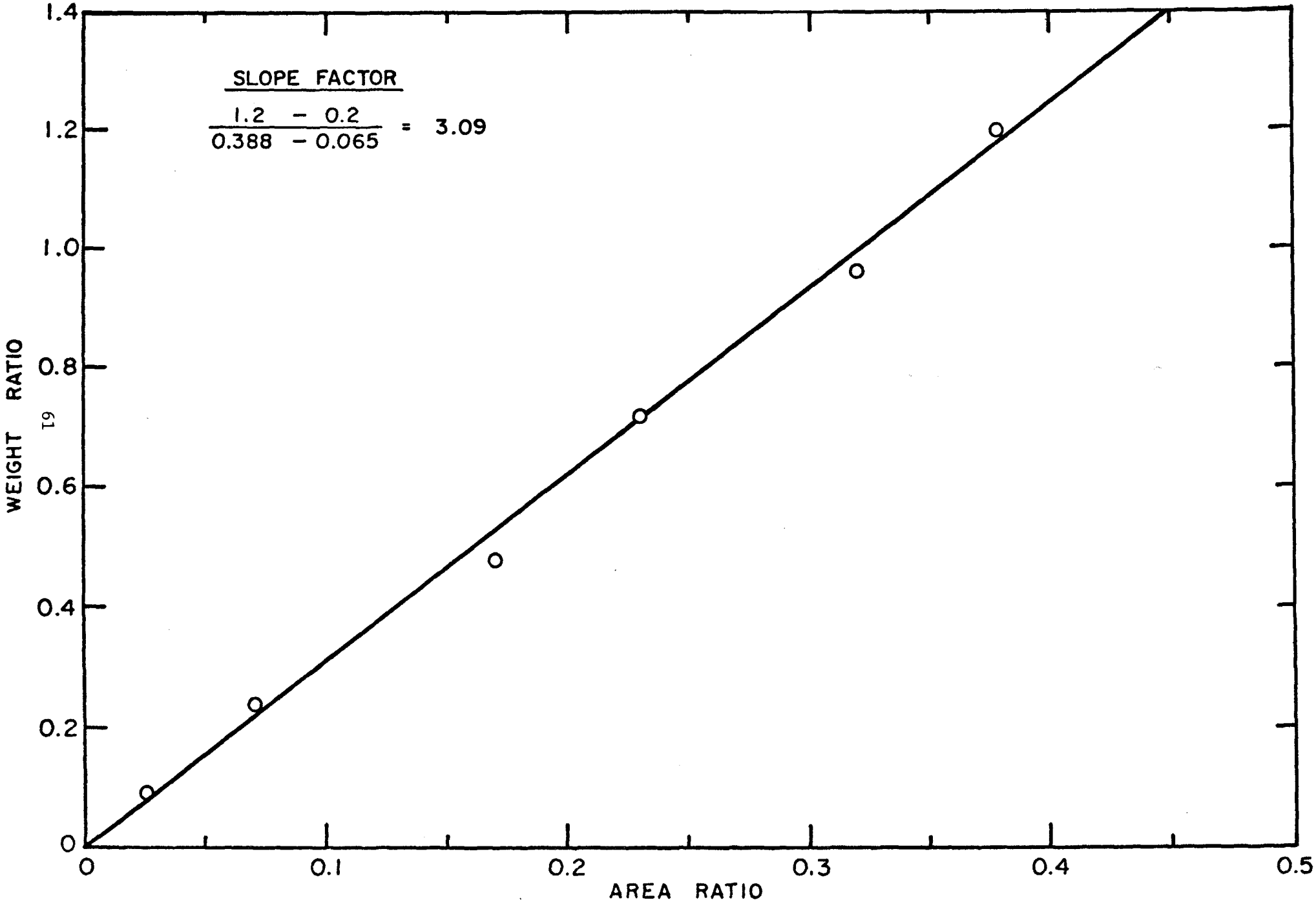

Figure 2. Calibration curve, moca in urine.

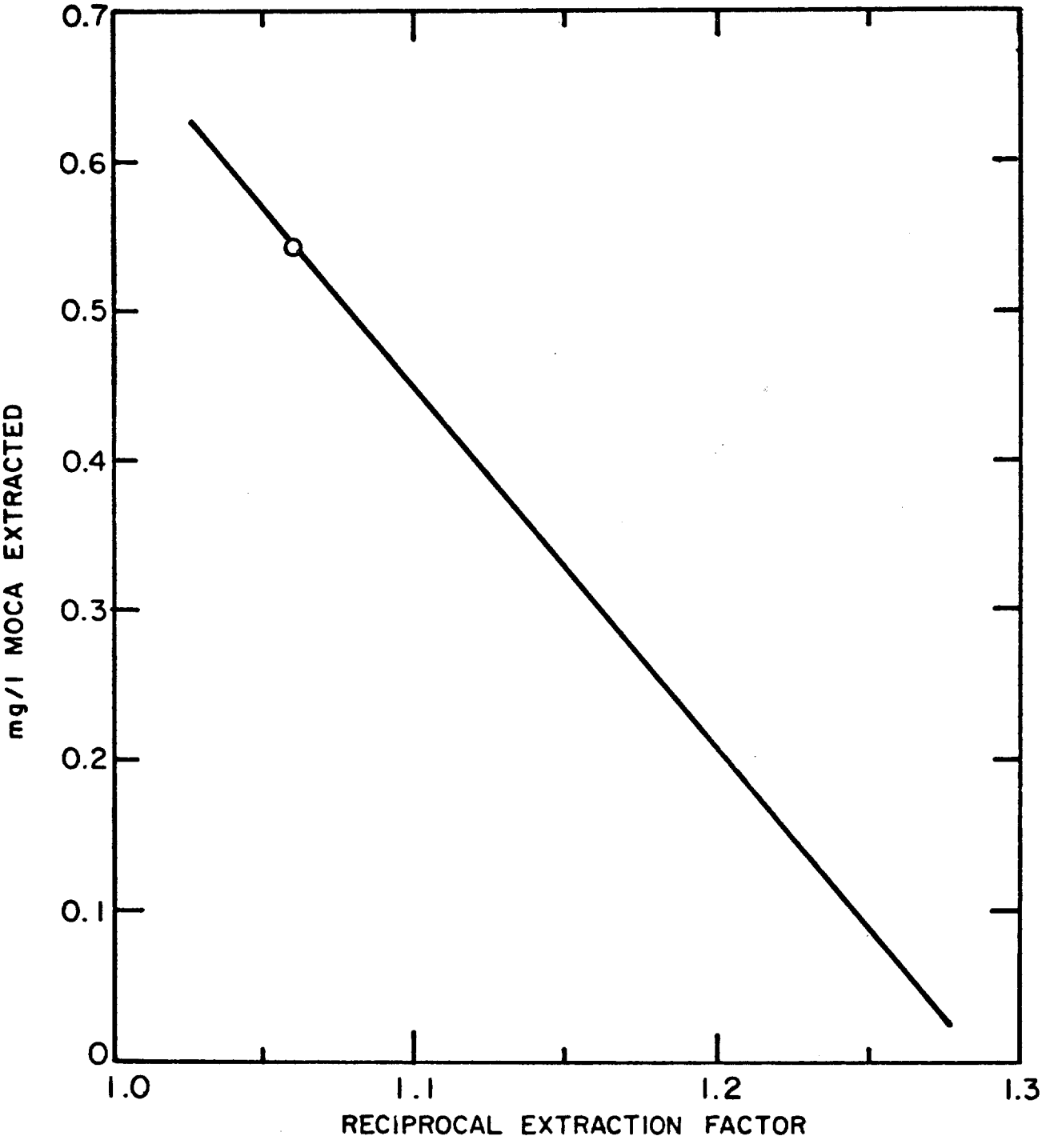

Figure 3. Extraction efficiency factor for MOCA in urine.

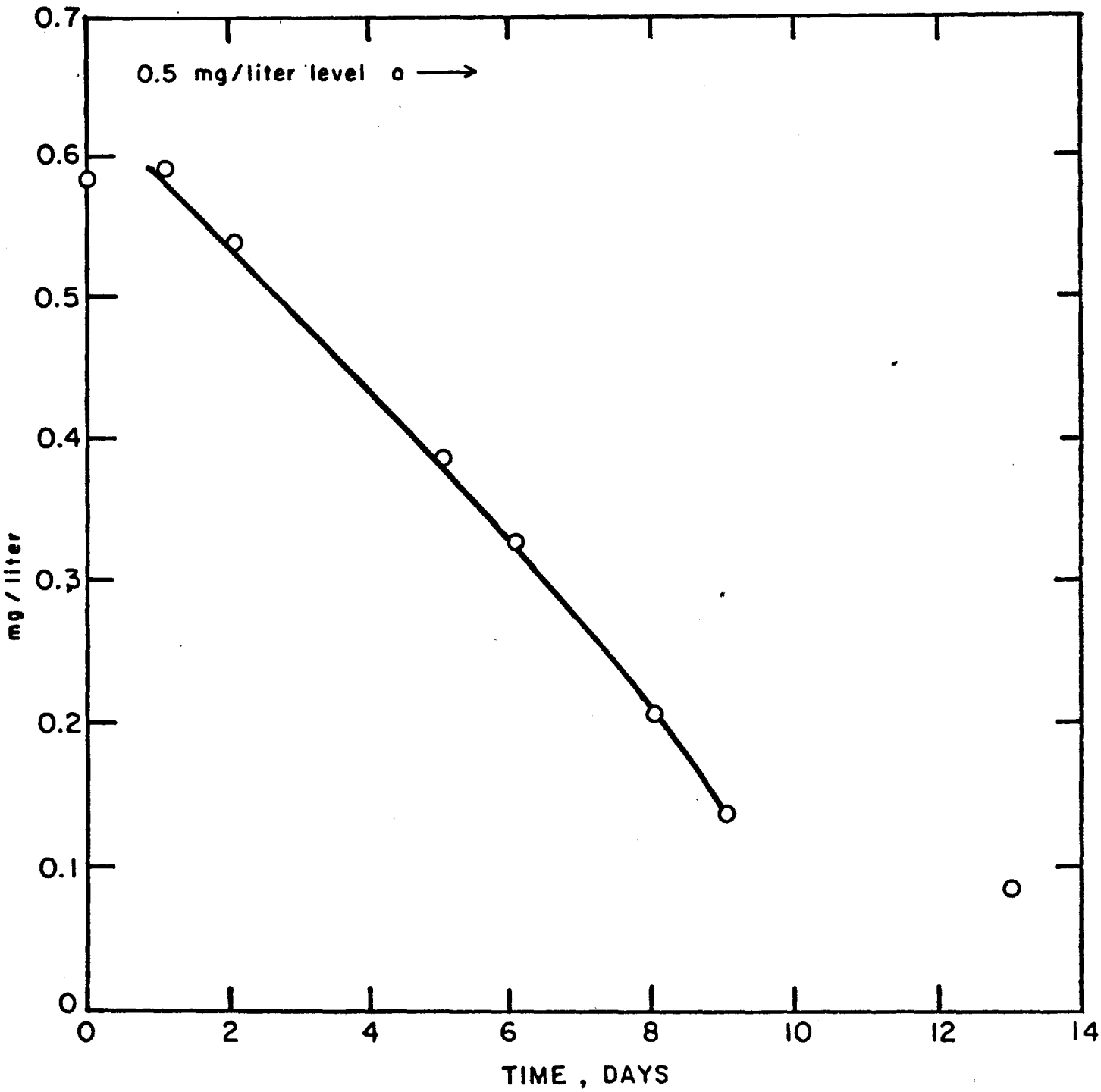

Figure 4. Moca in urine - degradation rate at room temperature.

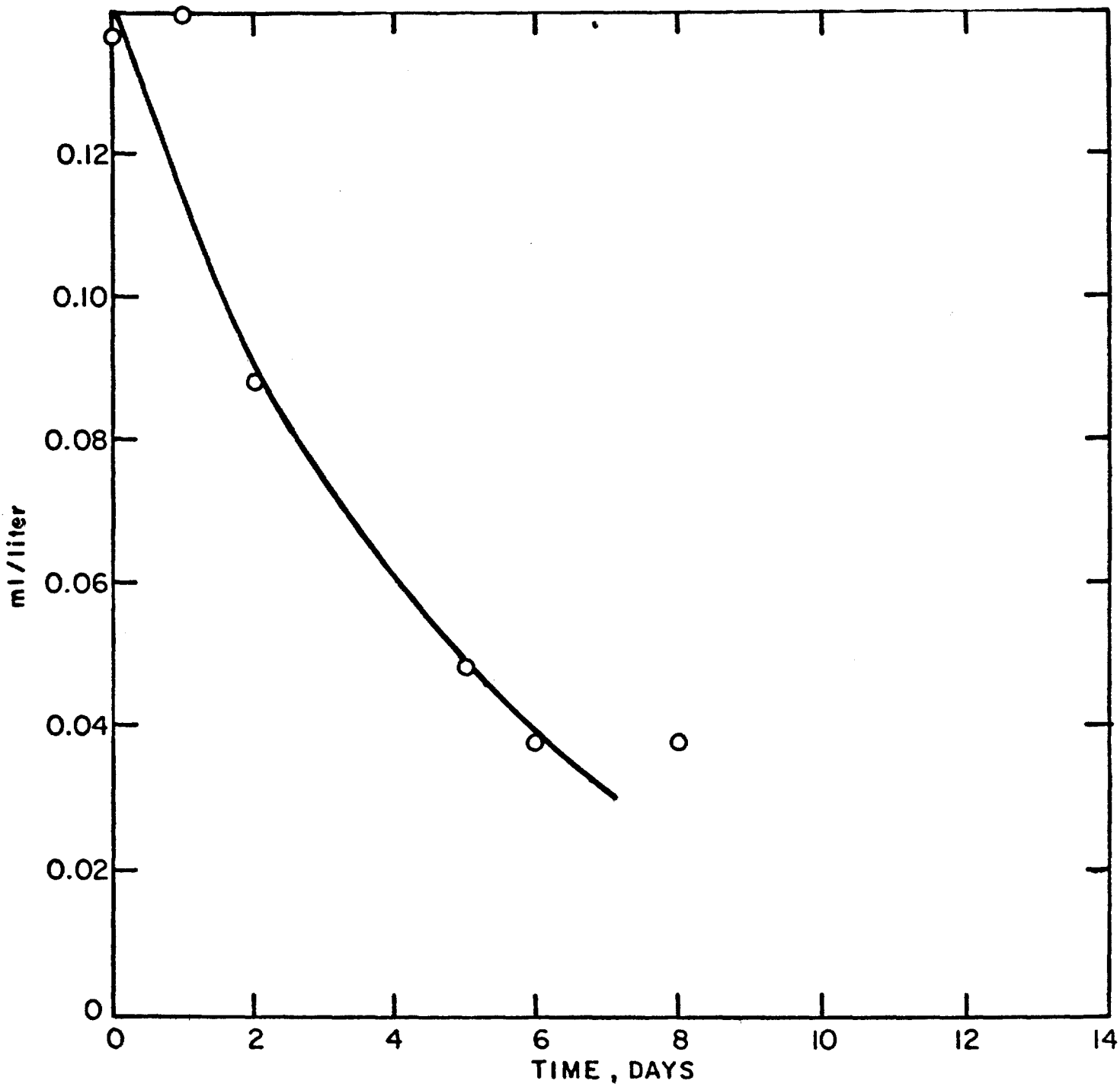

Figure 5. Moca in urine degradation rate at room temperature 0.1 mg/liter level .

APPENDIX IV.

METHOD FOR DETECTION OF MOCA (TM) CURING AGENT ON ENVIRONMENTAL SURFACES BY COLORIMETRIC SPOT TEST*

I. Scope and Application

This colorimetric method is applicable to the detection of MOCA on environmental surfaces and on protective clothing in the absence of other primary aromatic amines. The method is simple and can be readily used in the field.

II. Principle

The method is based upon the formation of a color complex by the reaction of the amine group of MOCA with nitrous acid to form the diazonium salt and subsequent coupling with itself. The nitrous acid is prepared "in situ" by reacting an aqueous solution of sodium nitrite with acetic acid.

III. Interferences

This method is a general colorimetric spot test for primary aromatic amines and not specific for MOCA.

Environmental surfaces and protective clothing may be contaminated with material which is colored originally. A positive test is one in which color is formed or increased after addition of the last reagent.

IV. Sensitivity, Precision, and Accuracy

The lower limit for the detection of MOCA using the colorimetric spot test was determined by swabbing an 0.05 sq. meter stainless steel area. Solutions of decreasing concentrations of MOCA were evaporated off the tray. The tray was then swabbed. The lower limit of one milligram per sq. meter gave readily seen color.

V. Apparatus

1. Cotton swabs

2. Glass vials

VI. Reagents (Reagent Grade)

1. Dimethylformamide (DMF)

2. Acetic acid

*This method is one employed by E.I. duPont de Nemours and Company, Inc., Elastomer Chemical Department, Wilmington, Delaware 19898, and is identified by their Code No. E350.5200S, 15 March 1976.

3. "Nitrite" solution

Dissolve 20 g sodium nitrite in 100 ml distilled water.

VII. Safety Precautions

1. DMF is rapidly absorbed through the skin and can carry other chemicals into the skin. DMF can pave the way for dermatitis. DMF is classified as a teratogen and females of childbearing age should not work with this chemical. If DMF comes in contact with the skin, wash well with water immediately.

2. Reagent grade acetic acid can cause serious burns and blisters to the skin. Wash well with water immediately if acetic acid is spilled on the skin.

3. MOCA may cause cancer based on tests with laboratory animals. Avoid skin contact and inhalation of vapor and dust. For details on safe handling practices, read bulletin AP 710.1.

VIII. Procedure

1. Place 10 ml of DMF in a glass vial.

2. Place a cotton swab into the glass vial containing DMF.

3. Wait 30 sec.

4. Wipe an area 8 in. x 10 in. with the cotton swab. Go over the area three times.

5. Place the cotton swab back into the DMF.

6. Wait 30 sec.

7. Add approximately 1 ml of acetic acid to the vial.

8. Add approximately 1 ml of "nitrite" solution to the vial.

9. Observe solution for development of an orange-brown color. The color which forms within 1 minute indicates that MOCA may be present (see Note 1).

IX. Notes

1. If the solution has color after swabbing, it is advisable to obtain two swabs of the same area (adjacent locations). One vial acts as a blank and compensates for any color pickup due to swabbing. The blank is treated exactly the same as the sample vial except that nitrite solution is not added. The two vials can be viewed side by side; any color increase in the nitrite treated sample can be easily noted.

A quantitative method for detection of certain carcinogens on metal, painted and concrete surfaces has been developed by Weeks, R.W. Jr., Dean, B.J. and Yasuda, S.K. and has been published in Analytical Chemistry Vol 48: 2227-2233, 1976.

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